12/08/23 Morning Report with @CPSolvers

"One life, so many dreams" Case Presenter: Vijay Balaji (@vijaybramhan) ***Case Discussants****: Rabih (@rabihmgeha) and Reza (@DxRxEdu)*

CC: 68 year old male with chronic fevers

HPI: In 2021 he noticed fevers with myalgia that lasted 2 months, given a short course of steroids and alternative medications, resulting in a mild reduction in fevers. 1 month later, patient was vaccinated for COVID-19, but still experienced recurrent fevers, and symptoms did not subside with steroids. Patient evaluated with imaging for fevers with blood tests - all normal. Received steroids for one month and fevers subsided, and from 201 until May 2023, patient was feeling well. In 2023 may he developed recurrent fevers, with similar pattern high grade fever, rigors. ROS negative for rash, joint pain, myalgia, headache, fatigue, and palpitations. Negative infectious work up of - HIV, HSV, anti HCV, brucella, bartonella. CT thorax showed mediastinal lymphadenopathy and splenomegaly. Non inflammatory work-up: ANA 1:100, RF, anti-ccp, ANCA negative. No improvement of fevers at this time, developed worsening condition and altered mental status. CBC showed HB 6.8, platelet 38,000, ferritin 1368, MCV 64, LDH 160, urea 40, Cr 2.4, ACE: 129, urine microscopy normal limits with no sediments or protein, CSF brain normal, multiple blood culture negative, calcium 11.4, PTH 4 (lab value 6), bone marrow cytopenia (hypocellular marrow with normal maturation with no atypical blasts). Diagnosed with sarcoidosis initially, however there was no histological evidence, transferred to an outside center, where patient responded to steroids and methotrexate, responded well. In October 2023, again he presented with recurrent fevers, despite optimized therapy (with steroids + MTX) with fevers and right sided chest pain. Since may until presentation, there was mild cytopenic presentation was present.

PMH: uncontrolled DM, Hypertension and Meniere's disease

Meds:

Soc Hx: Completed pilgrimage around India. Has no pets or cattle, however he has exposure to significant pigeons, performs daily actively and farming

Health-Related Behaviors: monogamous

Allergies: NKDA

Vitals: T: 103 **F HR:** 134 **BP:** 124/70 **RR:** wnl **SpO2** normal

Exam:

Gen and CV: noncontributory

Pulm: Right upper zone crackles

Abd: Moderate hepatosplenomegaly

Neuro: Paresthesias, nonspecific and no focal localization

Notable Labs & Imaging:

Hematology: CBC 9.9 WBC 2600 (neutrophil lymphocyte 7)

Chemistry: Na: 134 K: 4.2 Cl: BUN: urea 43 Cr: 0.98 glucose: Ca: 8.7 AST: 17 ALT: 65 Alk-P: 121 (normal), Alb 2.4
Ferritin (repeated) 1368, fibrinogen 424, triglycerides 147, urine microscopy normal, CD4 39%
Urinary antigen for Histoplasma 31 (strongly positive)

Imaging:
CXR: Right upper lobe consolidation
CT: hepatosplenomegaly, cavitary lung lesions, lymphadenopathy
Bone marrow: intracellular inclusions consistent with histoplasma started with amphotericin and despite optimal therapy patient continued to have persistent fevers.
RK39 antigen negative for leishmania, urinary antigen histo positive.
Persistent fevers resulting bronchoscopy paratracheal lymph nodes was positive for mycobacterium TB, started on anti-TB drugs and optimal dose of amphotericin. Later started on oral regiment after 10 days. Then was started on Itraconazole, but developed fevers on day 4. All doses were determined to adequate. During the persistent fevers, patient complained of a mild headache
Echocardiogram: no vegetations
Repeated immunoglobulin came back normal, CD4 count 401, 39% (lower normal), mild headache lead to a repeated MRI showed multiple ring enhancing lesions with central necrosis and cerebral abscess in the left temporal. ID consulted → suggested dose changes for current medications. 2 days ago after increasing amphotericin dose is afebrile.
Dx: Disseminated Histoplasmosis with superimposed TB infection

Problem Representation: 58 year old male with chronic fever, multiple environmental exposures with a previous diagnosis of Sarcoidosis, biopsy with histoplasmosis and BAL positive for TB.

Teaching Points (David):
- **Chronic fever**: points away from typical infections and prioritizes elusive infections (subacute endocarditis, osteomyelitis), unusual infections, autoimmune and malignancies
- **Clues to determine the etiology of the fever**:
++ Absence of pain and fatal consequences -> autoimmune?
++ Steroid-responsive -> autoimmune?
++ LAD and splenomegaly -> lymphoproliferative disorders?
++ Hypercalcemia, LAD, high ACE -> granulomatous processes?
++ Bicytopenia, high ferritin -> HLH?
- **Chronic reticuloendotelial activation** (hepatosplenomegaly, LAD, pancytopenia) -> think of **granulomatous diseases**: sarcoidosis, lymphomas, granulomatous infections (mycobacterial, endemic mycoses including histoplasmosis and talaromycosis)
++ Age makes sarcoidosis unlikely: it is very rarely diagnosed after 60.
++ Uncontrolled DM and exposures -> risk for infections (pigeons - Histo)
++ Intrapulmonary findings -> prioritize infections (lungs = the entrance door)
++ Hypercalcemia out of proportion to LAD makes Histo more likely than TB
- **Subacute cavitary lung lesion**:
++ Infections: lung abscess, mycobacterial, Nocardia, Actinomycosis, endemic mycoses, paragonimiasis,
++ Malignancy: 1º (squamous), 2º (mtx, lymphoma, Kaposi…)
++ Autoimmune: GPA, RA, aseptic abscess syndrome
- **Intracellular inclusions** -> more consistent with fungi. Mimickers:
++ Visceral leishmaniasis (rK39 Ag is very sensitive)
++ Chronic immune activation + BM inclusions -> VEXAS?
- Why not responsive to amphotericin? Not a fungus? Excess or deficit of immune activation? Uncontrolled foci?
*Indolent may not be so due to steroids.